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Review

A new hope in the management of hematologic malignancy: immunotherapy

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ABSTRACT

In recent years, Hodgkin's and Non-Hodgkin's lymphoma incidence is increasing all over the world. In the United States, lymphomas are the fourth most common malignancies among all. Lymphoid malignancies have a broad spectrum from mild indolent types, such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL), follicular lymphoma (FL), marginal zone lymphoma, and cutaneous T-cell lymphoma to aggressive types such as diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma, Burkitt's lymphoma, peripheral T-cell lymphoma. With better response rates to chemotherapy, longer disease-free survival and overall survival rates, lymphomas have satisfactory treatment results rather than solid organ tumors for oncologists. Throughout history, conventional chemotherapy agents, radiotherapy and their combinations have been used for the treatment of lymphoma. Especially, in the early stages of Hodgkin's lymphoma, a rate of 85-90% complete remission and high rate long-term remission can be achieved. However, despite this high response rate, 15-30% of patients are resistant to treatment. With current therapies response rate and persistent long-term remission rate in Non-Hodgkin's lymphomas are around 50%. Therefore, new therapeutic approaches such as immunotherapy and the using of cytotoxic properties of T cells against tumor has been developed and used in recent years for the treatment of refractory lymphoma.

Keywords: Hematologic malignancy, immunotherapy, new target

INTRODUCTION

Success of imatinib mesylate treatment abolished the need of allogeneic stem cell transplantation in chronic myeloid leukemia (CML) and also has guided the treatment of other hematologic malignancies. Especially the usage of Bruton's kinase inhibitors in CLL and indolent non-Hodgkin's lymphoma treatment has increased the response rates.[1]

T/B lymphocyte, macrophage, natural killer cell and cytokine mediated tumor immunology is a complex system that forms the basis of response against cancer. Primarily, perception of tumor cells as a foreigner and then proliferation of regulatory T lymphocytes to create a destroying microenvironment for tumor cells are necessary to create an initial response against cancer cells.[2]

Transfer of The Adaptive Immune Response and Chimeric Antigen Receptor (CAR) T Cell

One of the most effective treatment approaches is usage of CD19 specific, potential cytotoxic T cells which are programmed and created by genetic engineering, especially for the treatment of B-cell NHL and CLL. Mononuclear cells derived from peripheral blood accompanied by leukapheresis are collected and CD 19-specific T cells are isolated.[3] Several studies related to CAR T cell treatment has been conducted for the treatment of DLBCL and FL. In refractory FL patients, partial response achieved up to 32 weeks, by National Cancer Institute (NCI) researchers. In another study, 4 complete responses, 2 partial responses, and 1 stable disease symptoms achieved in 7 patients with DLBCL.[3,4]

CAR T cell treatment related side effects has been examined and there was no correlation between the rate of the infused T cells and the side-effect profile. Nevertheless, most important problems encountered was encephalopathy and B-cell aplasia. B cell recovery can occur in 6 months after infusion of T cells. Intravenous immunoglobulin support might be protective against infection, especially for the patients with B-cell aplasia.

Immunotherapy Aimed for Eliminating Immune Tolerance

For a long time, oncologists have dreaming to use the power of immune system to fight malignancies. Initial usage of immunotherapy for lymphomas began with thesis of graft versus tumor effect of T cells which were collected from the donor during allogeneic stem cell transplantation. After the discovery of rituximab treatment's efficacy, which acts against CD20 positive B cells, the idea of using immune agents in lymphoma treatment beside conventional chemotherapy has emerged, especially in non-Hodgkin's lymphomas.

Immunotherapy agents shows a wide variability from monoclonal antibody-based agents to transfer of adaptive

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immune response in cytotoxic T lymphocytes or inhibition of PD-1 (programmed cell death) receptors that prevents T cell activation.[1]

Immune checkpoint system leads to protection from self-tolerance and autoimmunity. Chronic antigenic stimulation of T cells via signaling through the PD-1 pathway is substantial. Once PD-1 stimulated by its ligands, T-cell proliferation, cytotoxicity, and cytokine production is decreased and apoptosis is increased. So, this interaction leads to generation and maintenance of peripheral tolerance.

In normal conditions, interaction of T cell receptors with antigen-presenting cells is necessary for immune system activation. In cancer patients, synthesis of proteins from cancer and non-cancer cells in microenvironment that suppresses T cell functions are increased, such as cytotoxic T Lymphocyte associated protein 4 (CTLA 4) and programmed cell death protein-1 (PD-1). The effect of PD-1 for the inhibition of T-cell activity seems to be stronger than by CTLA-4.[5]

Immune Checkpoint Inhibitors; Hodgkin's Lymphoma and Non-Hodgkin's Lymphomas

Although both CTLA 4 and PD-1 has an inhibitory effect on tumor immunity, they act with different mechanisms. CTLA 4 is particularly expressed in T cells in the lymph nodes. Mobilization of CTLA 4 is increased by CD28 stimulation via T-cell receptor signalization. Once CTLA 4 binds to CD80 and CD86 ligands, it blocks the communication between CD28 and T cell, thus inhibiting the T cell activation.[6]

PD-1 is particularly activated in extra nodal/ peripheral T cells and also their ligands on tumor cells. After PD-1 is activated and bounded to PD-L1 and PD-L2 receptors, phosphatidylinositol 3-kinase (PI3K) pathway is antagonized and T cell activation is blocked. The idea of increasing T cell activation by inhibiting PD-1 activity and decreasing the self-tolerance at lymphoid malignancies leads us to think that expression levels of PD-L1 and PD-L2 receptors may be effective in terms of response to treatment. PD-L1 expression occurs in hematopoietic cells such as T cells, B cells, macrophages, dendritic cells and natural killer cells and non-hematopoietic cells. PD-L1 expression is increased especially in Hodgkin Reed-Sternberg (HRS) cells through EBV related mechanisms, gene amplification, and chromosomal translocation in Hodgkin lymphoma. PD-L1 expression is also detected in Non-Hodgkin's lymphoma subtypes such as DLBCL, primary mediastinal B-cell lymphoma and anaplastic large cell lymphoma. 9p23-24 chromosomal amplifications are common in Hodgkin lymphoma patients and associated with good response to PD-1 inhibitor treatment.[7]

Pidilizumab is the first PD-1 inhibitor and particularly has been used for phase 1 and phase 2 studies in DLBCL patients. Although promising in refractory cases when combined with rituximab, desired success could not be achieved because of the low specificity of pidilizumab to PD-1 receptors. In phase 1 studies conducted with nivolumab and pembrolizumab, objective response rate was 36% and 40% in DLBCL and follicular lymphoma patients, respectively.[10] Most common side effects of PD-1 inhibitors are immune system associated pneumonia, colitis, hypophysitis, thyroiditis and hepatitis. The most serious side effects (grade 3 and 4) associated with immune checkpoint inhibitors, are most frequent with the ipilimumab treatment (20%). Immune-modulatory agents such as corticosteroids and infliximab could be used for the side effects of these agents.[8]

Today, frequency of PD-1 inhibitors usage is increasing, especially in relapsed Hodgkin lymphoma cases. Nivolumab has been used more often than pembrolizumab because of it's grade 1 and 2 treatment-related side effects. If the disease persists after autologous stem cell transplantation in relapsed/ refractory Hodgkin lymphoma patients, PD-1 inhibitor treatment seems to be preferred instead of allogeneic stem cell transplantation because of the difficulty of finding suitable donor and long-term strict control requirements.

Brentuximab Vedotin

Despite all the advances in the treatment, long-term remission can not be achieved at approximately 30% of classical Hodgkin lymphoma patients with conventional chemotherapy and radiotherapy.[9] In the present, standard treatment approach of these patients is high dose chemotherapy and autologous stem cell transplantation.[10] However, this treatment provides long-term remission for only 50% of patients and expected median survival time is 27 months for the rest. An antibody drug conjugate brentuximab vedotin is the only drug approved by the FDA in the last 30 years for this group of patients.

It selectively binds to CD30 (+) malignant HRS cells through chimeric monoclonal antibody in it's structure and shows tumoricidal effect by a microtubule inhibitor called as monomethyl auristatin E (MMAE).[11]

When compared with a phase 2 study consisting of 102 patients that conducted by Jones et al., this study also shows similar objective response rates (80% vs. 75%), at least in the early stages of disease.[12] However, PET/CT scan assessment after 6 cycles of treatment with brentuximab vedotin showed that, the objective response rate decreased up to 10% and progression of disease had observed in 7 patients with at least partial response in the early stages. This result demonstrated that brentuximab vedotin is insufficient to obtain long-term remission. In fact, decreasing of high objective response rates in further cycles that reached after the first 3 cycles of brentuximab vedotin treatment, revealed problem of permanent response rate with brentuximab treatment.[12,13]

Blinatumomab

Blinatumomab is a 55 kDa tyrosine protein derivative which is specific for CD3 and CD19 cells. So, it has immune effects on both T and B cells. Half-life of blinatumomab is 2 hours, therefore administration of 3 times a week is recommended in non-Hodgkin's lymphoma and CLL. Blinatumomab administration dose is 0.75-15 microgram/m² intravenously within 2-4 hours. In one study, blinatumomab was administered in doses of 15 microgram/m² in 76 patients with relapsed/refractory Non-Hodgkin's lymphoma (37% follicular lymphoma, 32% mantle cell lymphoma, 18% DLBCL and 12% others) and objective response rate and complete response rate was 69% and 37%, respectively.[14] While best response rate has detected in follicular lymphoma patients with a response rate of 80%, response rate in patients with DLBCL was 55%.[14] Blinatumomab was approved by FDA in December 2014 for refractory Non-Hodgkin's lymphoma treatment.

Small Molecule Inhibitors; Bruton's Tyrosine Kinase Inhibitors (BTKI)

B cell receptor signaling is essential for proliferation of normal and malignant B cells. B cell receptor expression is increased in DLBCL, FL, mantle cell lymphoma and CLL. Bruton kinase is a member of Tec kinase family and has a role in B cell receptor signal cascade with Syk and PI3K.

Ibrutinib

In a phase 3 open label randomized study that consisting of 391 patients with relapsed / refractory CLL or small lymphocytic lymphoma (SLL), 195 patients were randomly assigned to receive oral ibrutinib (420 mg once daily) and 196 patients randomly assigned to receive intravenous ofatumumab.[15] Median age was 67 (30-86) and all patients in both groups previously had a median of three-line treatment. Median follow-up time was 9.4 months and the overall survival rates at 12th month was 90% and 81% in ibrutinib and ofatumumab groups, respectively ($p<0.001$). Objective response rate was 42.6% in ibrutinib group and 4.1% in ofatumumab group ($p<0.001$). Most frequent treatment-related side effects in ibrutinib group was diarrhea, fatigue, pyrexia, and nausea. On the other side, side effects in ofatumumab group was fatigue and cough. Interestingly, development of cataract was seen 3% in ibrutinib group and 1% in ofatumumab group.

In another phase 2 multi-center study, efficacy of ibrutinib treatment (560 mg) was investigated in 111 relapsed or refractory mantle cell lymphoma patients.[16] Patients were enrolled into two groups: those who had previously received at least 2 cycles of bortezomib treatment and those who had previously received less than 2 complete cycles of bortezomib or had received no prior bortezomib treatment. The median age was 68 and patients had undergone a median of three (1-5) previous therapies. Objective response rate was 68% with a complete response rate of 21% and a partial response rate of 47%. Prior treatment with bortezomib had no effect on the response rate, and the median response duration was 17.5 months. Median progression-free survival was 13.9 months and overall survival rate was 58% at 18 months. Grade 3 or 4 side effects were infrequent, neutropenia and thrombocytopenia was detected in 16% and 10% of patients, respectively. As a conclusion ibrutinib shows efficacy in relapsed or refractory mantle cell lymphoma patients who received multiple prior therapies.

PI3K Inhibitors; Idelalisib

With activation of PI3K pathway, B cell receptor signaling becomes stronger especially in CLL patients. Idelalisib is a first-class selective inhibitor of PI3K pathway. Preclinical studies showed that idelalisib inhibiting PI3K-AKT pathway and inducing apoptosis.[17] Reliable side effect profile and anti-tumor activity of idelalisib shown with phase I and phase II studies in relapsed and refractory indolent NHL and CLL / SLL patients.

In a randomized, double blinded, placebo-controlled, phase 3 study consisting of 220 poor prognosed relapsed/ refractory CLL patients, one group received idelalisib in combination with rituximab and other group received rituximab plus placebo. Objective response rate was 81% in idelalisib group and 13% in placebo group ($p<0.001$). Overall survival at 12 months was 92% in idelalisib group and 80% in placebo group ($p<0.02$). Median progression-free survival was 5.5 months in the placebo group and was not reached in the idelalisib group yet ($p< 0.001$).[18]

Idelalisib received FDA approval in July 2014 for treatment of relapsed CLL and SLL patients who received at least 2 prior therapies.

Immunomodulators; Lenalidomide

Mantle cell lymphoma is 6% of all NHLs and has a heterogeneous clinical presentation. Wait and see policy may be preferred in indolent forms, but in aggressive forms immediate high-dose chemotherapy following induction treatment and allogeneic stem cell transplantation seems to be the ideal approach. New therapeutic agents in resistant and aggressive mantle cell lymphoma patients remain promising. Lenalidomide is an immunomodulator agent and successful response rates was obtained in multiple myeloma (MM) and myelodysplastic syndrome patients. Efficacy of lenalidomide in lymphomas was shown in preclinical studies conducted in guidance of this knowledge. Better response rates (53% vs. 35%) and long term response rates (16.3 vs. 13.7 months) were provided in mantle cell lymphoma patients rather than other subgroups in a phase II study with NHL patients.[19]

In MCL-001 (EMERGE) study,[20] efficacy of lenalidomide (administered 5 mg per oral on days 1 through 21 in every 28 days) examined in 134 mantle cell lymphoma patients who were refractory to prior immunochemotherapy and bortezomib. Median age was 67 (43-83), median of prior therapies was 4 (2-10), objective response rate was 28% (8% partial response, 20% partial response), median duration of response was 16.6 months, median progression free survival was 4 months and median overall survival was 19 months. The most common adverse effects was neutropenia (43%), thrombocytopenia (28%), anemia (11%) and pneumonia (8%).

Lenalidomide received FDA approval in June 2013 for treatment of relapsed mantle cell lymphoma patients after 2 prior therapies.

Proteasome Pathway Inhibitors; Bortezomib, Carfilzomib

MM is 1% of all cancers and 10% of all hematologic malignancies. Not only genetic mutations in plasma cells but also bone marrow microenvironment and most importantly, the loss of strength of the immune system to fight against tumor is responsible for progression in MM patients. Although B cell disorders is seen in MM primarily, T cell functional defects also has been observed. Especially, loss of tumor-specific CD4 and CD8 T cells and natural killer cells in monoclonal gammopathy of undetermined significance (MGUS) patients is seems to be responsible for progression of disease to MM. In the light of these findings use of new immunologic agents for treatment of MM brings the success of treatment with itself.

Ubiquitin-Proteasome pathway is responsible for degradation and elimination of damaged proteins in healthy cells to ensure the healthy cell cycle. Protein synthesis cycle is required for cell life and energy is provided by proteasomes. It has been shown that the usege of proteasome inhibitors in MM, mantle cell lymphoma and some types of leukemia, induce apoptosis and inhibits uncontrolled cellular proliferation.[21] Dexamethasone and bortezomib combination is more effective and well tolerated in MM patients than vincristine, adriamycin, dexamethasone (VAD) combination and seems to be better choice as a first line treatment.[22]

Carfilzomib is a second-generation proteasome inhibitor with selective and irreversible inhibition of pathway and approved by FDA for the usege in treatment of in refractory MM patients.

A summary of Immunotherapeutic agents is given in **Figure 1**.

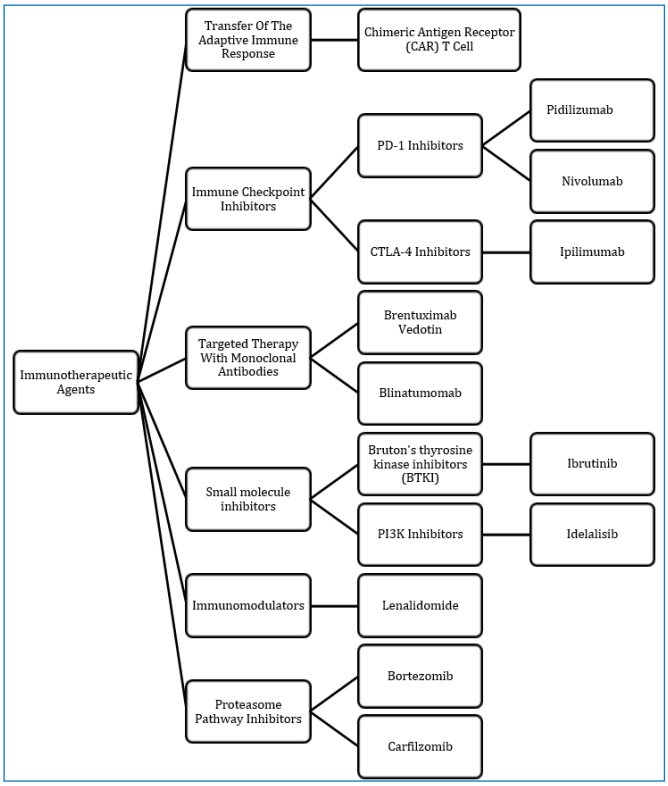

Figure 1. Immunotherapeutic agents

CONCLUSION

Immunotherapy has lead the oncology science into a new era, and hematologic malignancies seems to be the leading group that benefits. Immunotherapeutic approaches had stunning effects at the treatment of some solid tumors, as well as some types of hematologic cancers. There are numerous possible combinations of new drugs to test their efficacy in many tumors and settings. Therefore, the spectrum of immunotherapy is vast and enticing. However, to maximize the therapeutic potential of these strategies, much studies remains to be done in a coordinated fashion.

ETHICAL DECLARATIONS

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